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Task 3. Analogs of Tetrahydrocannabinol

for

Chemical Corps Procurement Agency

Project No. 4-08-03-001

Contract No. CML-4564

Progress Report

from

December, 1953 thru January, 1954

[redacted]

SHELL DEVELOPMENT COMPANY
EMERYVILLE, CALIFORNIA

Bi-Monthly Report No. 9

on

[redacted]

TASK 3

for

Chemical Corps Procurement Agency

Contract No. CML-4564

Period Covered: December, 1953 through January, 1954

Reported and Reviewed: D.E. Winkler
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Approved: W.E. Vaughan

SHELL DEVELOPMENT COMPANY
EMERYVILLE, CALIFORNIA

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Abstract

A thiopyran analog of tetrahydrocannabinol has been prepared in which the amyl group in the three position (I) has been substituted by methyl. The corresponding oxygen analog has been prepared as a reference standard.

The synthesis of a compound having an aminoethyl group in the three position has been carried to what is believed to be 1-hydroxy-9-methyl-7,8,9,10-tetrahydro-6-dibenzopyrone-3-acetic acid.

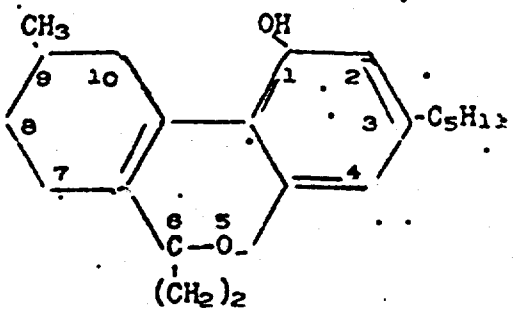
Another unsuccessful attempt was made to prepare a compound with an amino group in the one position.

The work on Task 3 is terminated with this report.

Analogs of Tetrahydrocannabinol

Nitrogen Analogs

Another attempt has been made to prepare a nitrogen analog of tetrahydrocannabinol (I) having a dimethylamino group in the one position.[a]

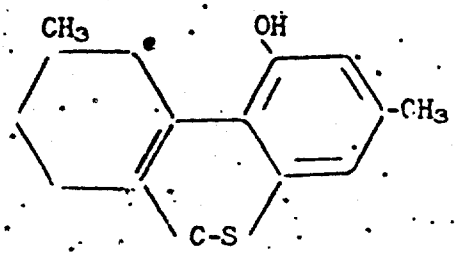


(I)

The method tried involved the reaction of ethyl 5-methyl-cyclohexanone-2-carboxylate with 3-dimethylamino-5-amylphenol according to Long and Sears[b] who use zinc chloride to effect the condensation of keto esters with m-dialkylaminophenol. The reaction was tried with and without a solvent - the two methods suggested in the patent. When a solvent was used the starting materials were recovered unchanged. Without a solvent a higher boiling material was produced which boiled over a wide range and was never successfully purified. The patent claims were tested by reacting our keto ester with m-dimethylaminophenol and a crystalline material was recovered. Ring closure probably did not occur between the amino and hydroxyl group but rather para to the amino group.

Sulfur Analogs

Since the preparation of 3-mercapto-5-amylphenol appeared improbable at this time,[c] and it was possible to prepare 3-mercapto-5-methylphenol, it was decided to prepare a sulfur analog (II) having a methyl group in place of amyl in the three position.



(II)

a) Winkler, D.E., Progress Report 8 (1953).
b) Long, R.S.; and Sears, C.A. (to American Cyanamid Co.) U.S. Patent 2,647,132.
c) Winkler, D.E., Progress Report 9 (1953).

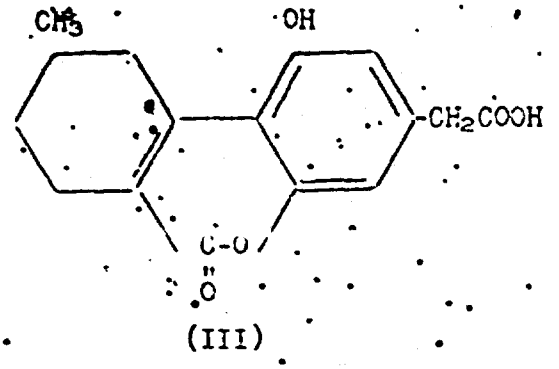
This sulfur derivative was prepared by first adding 3-mercapto-5-methylphenol to pulegone to form a thioether[a] and then cyclizing by refluxing in benzene solution with phosphorus oxychloride. We feel certain that the thioether and not the oxygen ether is formed in the first step in the above reaction for it has been demonstrated that phenol does not add to pulegone under the conditions used for adding the mercaptan group. The low sulfur value (85% of theory) for our final compound is probably due to the presence of arcinol in the 3-mercapto-5-methylphenol, which could have been formed during the diazotization of 3-amino-5-methylphenol. During the cyclization of the thicether the arcinol would have reacted with pulegone to form 1-hydroxy-3,6,6,9-tetramethyl-7,8,9,10-tetrahydro-6-dibenzopyran which is probably the impurity in our thiopyran. A better product might have been obtained if the thioether had been distilled before cyclization.

An alternate route to the thiopyran which involved the reaction of ethyl 5-methylcyclohexanone-2-carboxylate with 3-mercapto-5-methylphenol was tried but the yield of thiopyrone was too low to be attractive, so the conversion to thiopyran was not attempted.

To obtain a reference standard for use with the sulfur compound the oxygen analog was prepared by reacting the usual keto ester with orcinol to form a crystalline pyrone which was purified and converted to the pyran with methyl magnesium iodide.

Changes in Alkyl Groups

In a previous report[b] the start of the synthesis of a compound having an aminoethyl group in the three position of tetrahydrocannabinol (I) was described. At that time the synthesis was at the stage of 3,5-dimethoxyphenylacetic acid. This acid has now been converted to 3,5-dihydroxyphenylacetic acid, which has been condensed with ethyl 5-methyl-cyclohexanone-2-carboxylate in the presence of 80% sulfuric acid to form a crystalline material whose analysis is consistant with (III). Termination of the task has prevented further work.



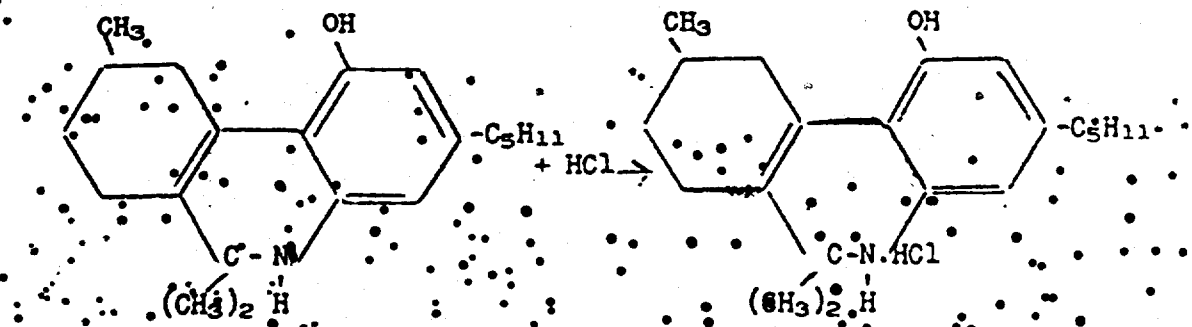
(III)

a) Winkler, D.E., Progress Report 7 (1953).
b) Winkler, D.E., Progress Report 8 (1953).

For an alternate route, 3,5-dihydroxyphenylacetic acid has been condensed with pulegone. An acidic material of higher molecular weight was recovered but due to the termination of the project it has not yet been purified.

APPENDIX

1-Hydroxy-3-n-Amyl-6,6,9-Trimethyl-7,8,9,10-Tetrahydrophenanthridine Hydrochloride, $C_{21}H_{32}ONCl$

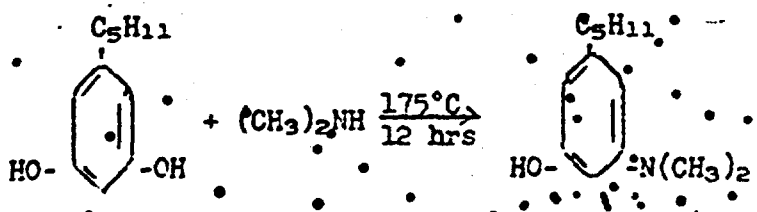


An excess of gaseous HCl was passed into a solution of 52 g of 1-hydroxy-3-n-amyl-6,6,9-trimethyl-7,8,9,10-tetrahydrophenanthridine in 1000 g of benzene at room temperature. The hydrochloride precipitated as a viscous oil from which the HCl saturated benzene was decanted after three hours at room temperature. The phenanthridine hydrochloride was oven dried to an amorphous solid. The yield was 57 g or 98%.

Anal calc'd for $C_{21}H_{32}ONCl$: C, 72.0; H, 9.22; N, 4.00; Cl, 10.13.
Found: C, 71.1; H, 9.3 ; N, 3.9 ; ionic Cl, 10.1.

3-Dimethylamino-5-Amylphenol. $C_{13}H_{21}ON$

bp 141-5°C/0.2 mm

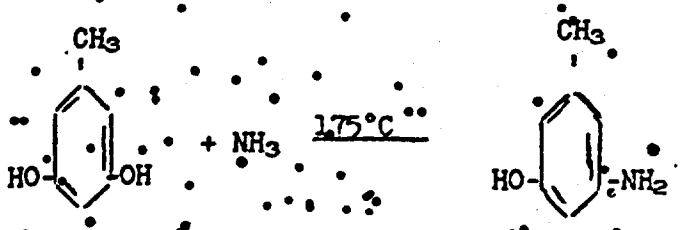


A mixture of 35 g. of amyl-3,5-dihydroxybenzene, 27 g of dimethyl amine, 40 g of water and 12 g of 85% phosphoric acid was shaken in a steel bomb for twelve hours at 175°C. The excess dimethyl amine was removed under vacuum, and the product dissolved in 500 ml of ether and extracted with 500 ml of 1NHCl. The amine was sprung by adding sodium bicarbonate, extracted with ether, washed with water and Claisen distilled. A 50% conversion to product was recovered.

Anal calc'd for $C_{13}H_{21}ON$: C, 75.3; H, 10.2; N, 6.76.
Found: C, 74.9; H, 9.9; N, 6.5.

3-Amino-5-Methylphenol, C_7H_9ON

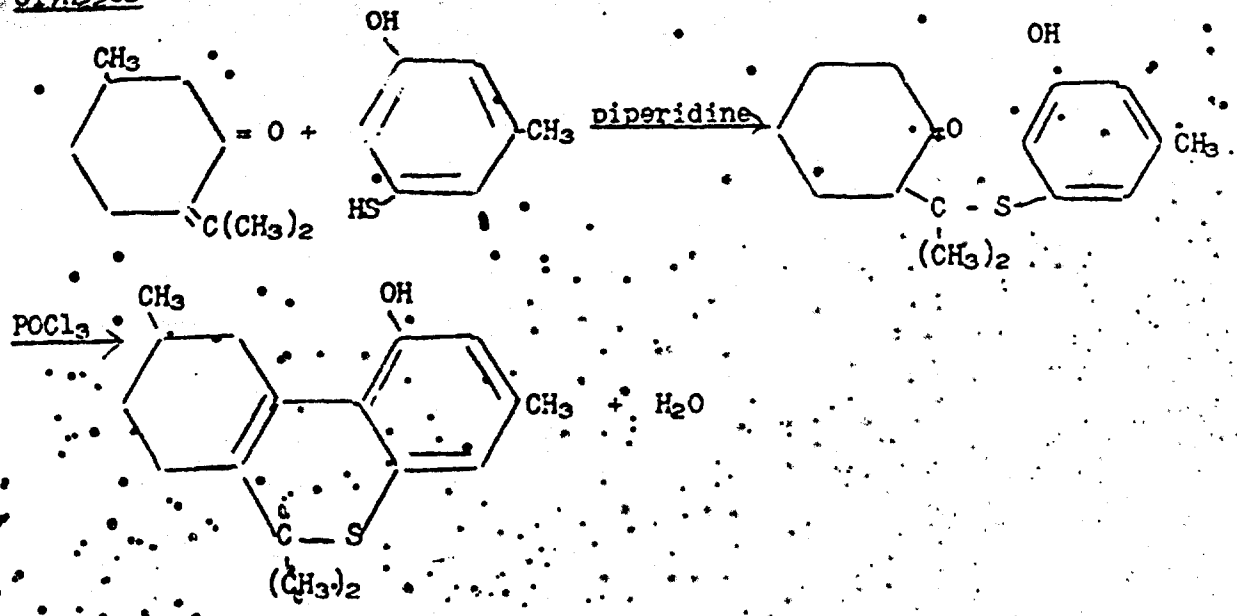
mp 135-6°C



A solution of 192 g of orcinol, 112 g of diammonium phosphate, 200 ml of 28% ammonium hydroxide, and 300 ml of water was shaken in a steel bomb for 12 hours at 175°C. The excess ammonia was removed under vacuum, and the product taken up in 1 l of ether and extracted with 150 ml of concentrated HCl in 1 l of water. The 3-amino-5-methylphenol was sprung from the acid solution with sodium bicarbonate, and after cooling, filtering, washing, and drying, 154 g (80% yield) of product was recovered. It can be purified by recrystallization from water.

Anal calc'd for C_7H_9ON: N, 11.37
Found: N, 11.2

1-Hydroxy-3,6,6,9-Tetramethyl-7,8,9,10-Tetrahydro-6-Dibenzothiopyran, bp 160-180°C/0.02 mm
$C_{17}H_{22}OS$



A solution of 47 g (0.34 mol) of 3-mercapto-5-methylphenol, 51 g (0.34 mol) of pulegone and 2 ml of piperidine was allowed to stand overnight at room temperature and then heated for four hours at 100°C. The thioether was taken up in 600 ml of benzene, washed twice with water, dried under a phase separating head, and after adding 17 ml (0.18 mol) of $POCl_3$ it was refluxed gently for nine hours in a water bath. The product was then washed thoroughly with water and distilled. A precut was discarded and the fraction boiling at 160-180°C at 0.02 mm was collected. The low sulfur value is believed to be due to the presence of 1-hydroxy-3,6,6,9-tetramethyl-7,8,9,10-tetrahydro-6-dibenzopyran as explained in the body of this report.

Anal calc'd for $C_{17}H_{22}OS$: C, 74.3; H, 8.08; S, 11.7.
Found: C, 74.5; H, 8.1 ; S, 9.9.

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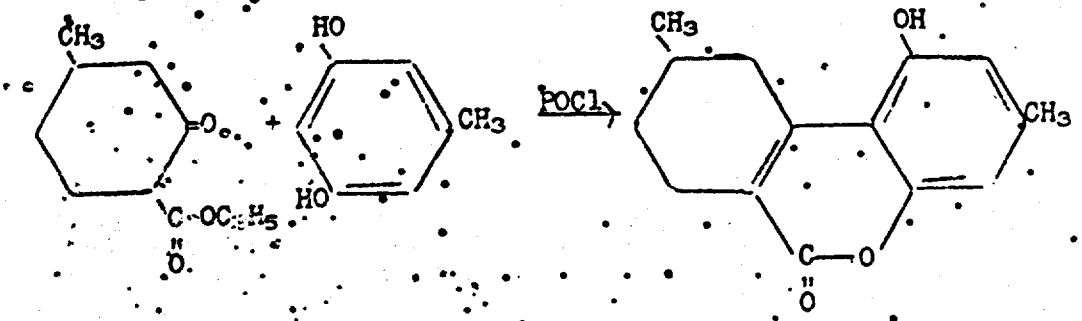
1-Hydroxy-3,9-Dimethyl-7,8,9,10-Tetrahydro-6-Dibenzopyrone, $C_{15}H_{16}O_3$

mp 256-7°C



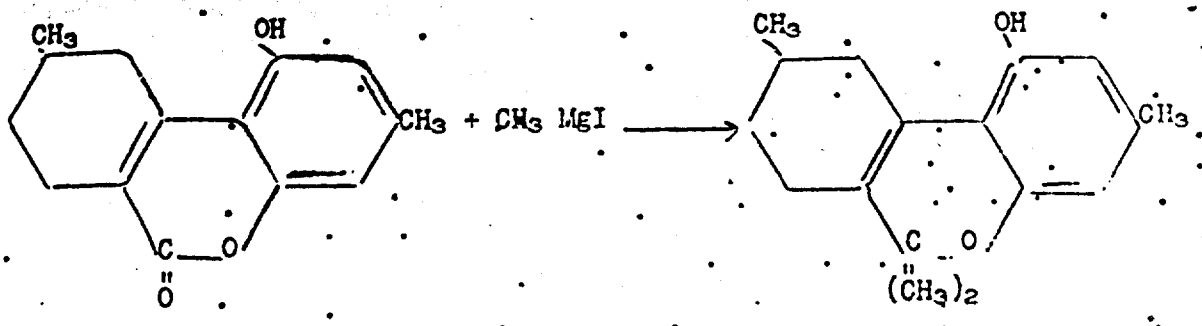
The procedure of Adams and Baker[a] was followed with the exception that equal molar amounts of keto ester, orcinol, and $POCl_3$ were used. A 70% yield of product, recrystallized from ethanol, was recovered. The highest melting point which we were able to obtain on an aluminum block was 256-7°C. Adams[a] reported 262-3°C.

Anal Calc'd for $C_{15}H_{16}O_3$: C, 73.7; H, 6.62
Found: C, 73.2; H, 6.6

a) Adams, R., and Baker, B.R., J Am Chem Soc 62 2408 (1940).

1-Hydroxy-3,6,6,9-Tetramethyl-7,8,9,10-Tetrahydro-6-Dibenzopyran, $C_{17}H_{22}O_2$

bp 145-155°C/0.02 mm



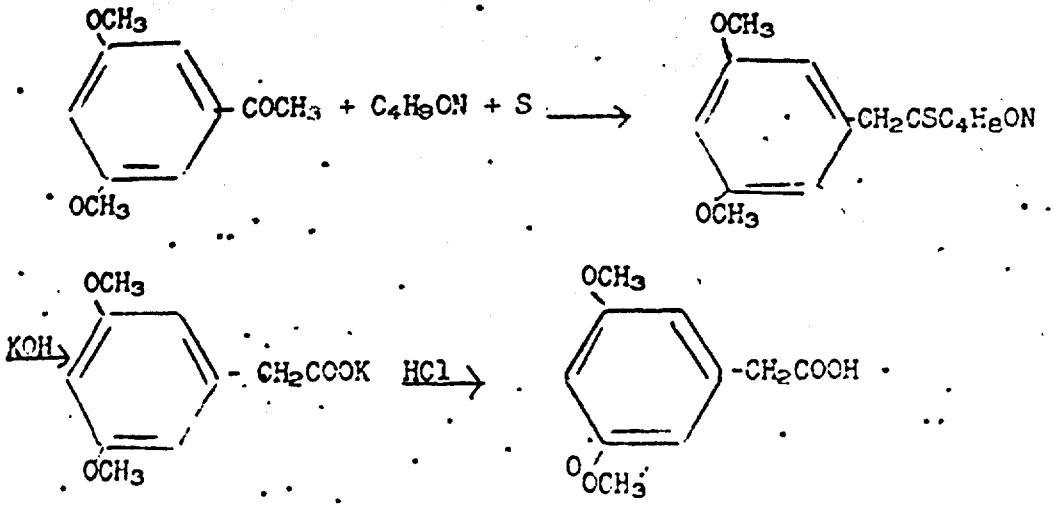
The procedure followed was similar to that used in the preparation of 1-hydroxy-3-secondary nonyl-6,6,9-trimethyl-7,8,9,10-tetrahydro-6-dibenzopyran.[a)]

Anal calc'd for $C_{17}H_{22}O_2$: C, 79.0; H, 8.60.
Found: C, 78.7; H, 8.6

a) Winkler, D.E., Progress Report 4 (1953).

3,5-Dimethoxyphenylacetic Acid, $C_{10}H_{12}O_4$

mp 100.5-101°C



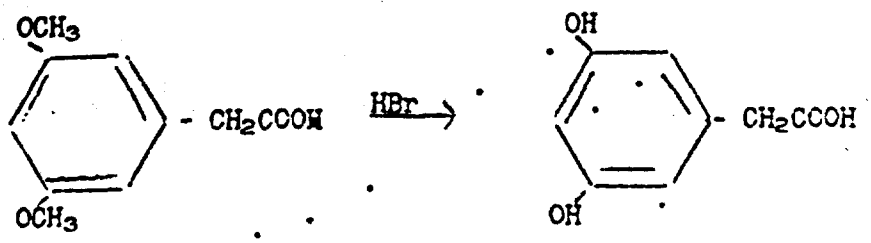
The Kindler modification of the Willgerodt reaction as used by Newmann[a] and Schwenk[b] was employed for this synthesis. A mixture of 50.5 g (0.28 mol) of 3,5-dimethoxyphenyl methyl ketone,[c] 13.5 g (0.42 mol) of sulfur and 36.5 g (0.42 mol) of morpholine was brought slowly to boiling and then refluxed fourteen hours. The crude thiomorpholide was hydrolyzed by refluxing for twelve hours with 74 g of KOH in 740 ml of water. After springing with HCl, the crude acid was filtered and purified by recrystallizing from water with the aid of decolorizing carbon. A 69% yield of acid was recovered.

Anal calc'd for $C_{10}H_{12}O_4$: C, 61.2; H, 6.17
Found: C, 60.9; H, 6.2

a) Newmann, M.S., J Org Chem 9 521 (1944).
b) Schwenk, E., and Bloch, E., J Am Chem Soc 64 3051 (1942).
c) Preparation similar to butyl ketone, Winkler, D.E., Progress Report 5 (1953).

3,5-Dihydroxyphenylacetic Acid, $C_8H_8O_4$

mp 128-128.5°C



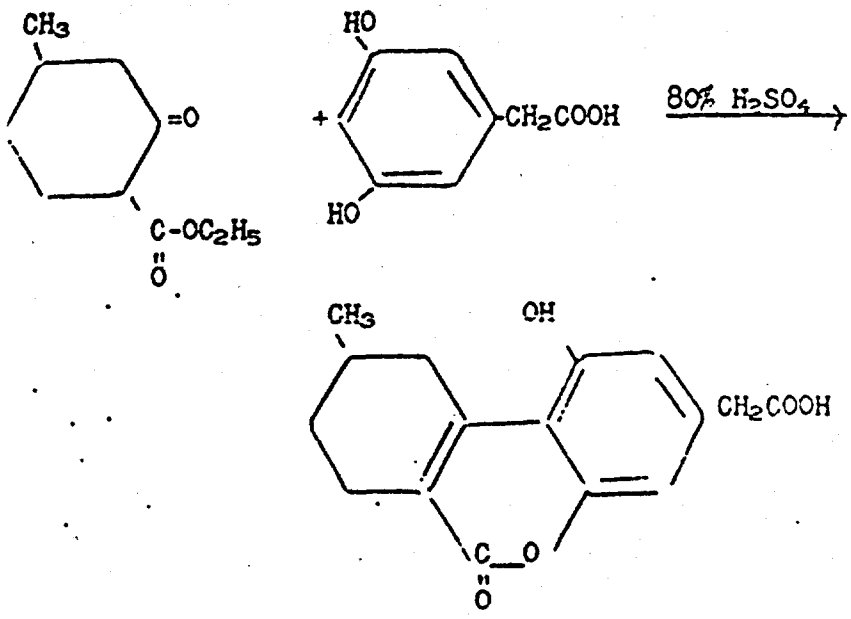
A solution of 85 g (0.43 mol) of 3,5-dimethoxyphenylacetic acid, 440 ml of 48% HBr, 440 ml of acetic acid, and 42 ml of HI (sp gr, 1.7) was refluxed for 16 hours according to the method of Levine[a] for the preparation of o-hydroxyphenylacetic acid. About half of the solvent was removed under vacuum and the remainder diluted with 1 l of water and extracted with three 1 l portions of ether. An 83% yield of crude acid was obtained which could be purified by dissolving in ethyl acetate and precipitating with benzene or chloroform.

Anal calc'd for $C_8H_8O_4$: C, 57.1, H, 4.80.
Found: C, 57.2, H, 4.9

a) Levine, J., Elbe, T.E., and Fischbach, H., J Am Chem Soc 70 1930 (1948).

1-Hydroxy-9-Methyl-7,8,9,10-Tetrahydro-6-Dibenzopyrone-3-Acetic Acid, $C_{16}H_{16}O_5$

mp 240-41°C



The method of Desai[a] for the condensation of methyl β-resorcylate with ethyl cyclohexanone-2-carboxylate was used.

A solution of 2.0 g of 3,5-dihydroxy-phenylacetic acid and 2.0 g of ethyl 5-methylcyclohexanone-2-carboxylate in 20 g of 80% sulfuric acid was allowed to stand five days at room temperature. Upon pouring into 200 g of ice and water a precipitate formed which was filtered and washed. The yield was 3 g of crude material. After three recrystallizations from 40% ethanol, 1.0 g was recovered which melted at 240-41°C.

Anal calc'd for $C_{16}H_{16}O_5$: C, 66.7, H, 5.60.
Found: C, 66.4, H, 5.5.

a) Desai, R.D., Gaitonde, M.M., Mehdi Hanson, S., and Shah, R.C., Indian Acad of Sci 25 345 (1947).